REMARKS

Applicant has updated the priority claim as requested by the Examiner.

1. Lack of written description under 35 USC 112(1)

Claims 1, 3 – 7 and 21 – 27 stand rejected under 35 USC 112(1). The Examiner states, in paragraph 5 of the Office Action, that the specification does not contain a representative list of autoantigens and that applicant has claimed a "broad genus of fusion proteins that contain T cell receptor antagonists, with the identity of the antagonists being defined only through their activity as an antagonist of autoreactive T cells." Applicant respectfully disagrees with the rejection.

There is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed. MPEP 2163 II.A; In re Wertheim, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). Consequently, rejection of the original claim should be rare. The inquiry into whether the written description is met is a question of fact that must be determined on a case by case basis and depends on the nature of the knowledge imparted to those skilled in the art by the disclosure. MPEP 2163 II.A; In re Wertheim, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976).

Applicant's claims are directed to a fusion protein "comprising an immunoglobulin or portion thereof linked to one or more T cell receptor antagonists ...." Thus the claimed fusion protein is not of a broad genus but is comprised of an immunoglobulin, or portion thereof, comprising at least part of a "constant region [fc region] of an immunoglobulin molecule" capable of "binding to an Fc receptor of an antigen presenting cell." In addition, the fusion protein must also be linked to "one or more T cell receptor antagonists." Thus the wording of the claim does not encompass a broad genus of fusion proteins but instead to a fusion protein where most of the fusion protein has a predictable structure, i.e., an "immunoglobulin" or "portion thereof" capable of binding to an Fc receptor (which requires a conserved Fc portion) of an antigen presenting cell. In addition, the fusion protein must be linked to one or more T cell receptor antagonists, many of which are known to one of ordinary skill in the art. While applicant does not at all agree with the rejection, to expedite examination and to clarify the claimed invention, applicant has limited the number of autoimmune disorders mentioned in the claims to multiple sclerosis, rheumatoid arthritis

and insulin dependent diabetes in claim 1. In claim 6, three additional autoimmune disorders are listed. In claim 21, applicant has limited the claim to two autoimmune disorders and in claim 23 four additional autoimmune disorders are listed. Thus, applicant believes that there is ample written support in the specification for the claimed invention.

According to the case cited in the Office Action, of University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (CAFC 1997), whether the specification shows that an applicant was in possession of the claimed invention is not a single or simple determination but is a factual determination reached by considering multiple factors. Factors include the level of ordinary skill in the art, partial structure, physical or chemical properties, functional characteristics alone or a disclosed correlation between structure and function, and the method of making the claimed invention. University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (CAFC 1997). Applicant has disclosed two such T cell receptor antagonists, the specification teaches how to make the claimed invention and functional characteristics are well defined. Applicant has also narrowed the number of autoimmune disorders to a limited number. Applicant therefore respectfully submits that the claims are allowable as having adequate written support under 35 USC 112(1).

2. Lack of Enablement under 35 USC 112(1)

Claims 1, 3 – 7 and 21 – 27 stand rejected under 35 USC 112(1) because, as stated in the Office Action, the specification, while being enabling for the alleviation of autoimmune symptoms in the murine EAE model, does not reasonably provide enablement for the alleviation of symptoms associated with any autoimmune disorder.

As mentioned in regard to the rejection of the claims for lack of written description, the claims are no longer directed for alleviation of symptoms with any autoimmune disorder but are now directed to a limited number of T cell mediated autoimmune disorders. However, applicant believes that the claims were enabled as filed.

The PTO claims that "insufficient guidance is provided concerning the identity of the antagonist to be used in the claimed diseases other than for antagonists derived from proteolipid and

myelin basic protein." Applicant respectfully disagrees. The enablement requirement requires that the specification describe how to make and use the claimed invention. The specification clearly teaches how to make the claimed constructs and much of the claimed fusion protein is of a predictable structure since it is composed of an immunoglobulin or a portion thereof. Regarding inserting the T cell receptor antagonist into the composition, one would follow the procedures stated in the specification. Regarding identifying the appropriate T cell receptor antagonist for the listed autoimmune disorders, one of ordinary skill in the art could readily indentify appropriate peptides as stated in the literature or with routine experimentation. The standard for determining whether the specification meets the enablement requirement is well known. It is not whether there is some experimentation involved, but whether or not the experimentation is undue. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (CAFC 1988); Mineral Separation v. Hyde, 242 U.S. 261, 270 (1916). There is little question that based upon the considerable guidance in making and using the claimed fusion proteins as stated in the specification, that it would not require undue experimentation to make and use the claimed invention based on the factors mentioned in Wands.

The Examiner cites the Pender and Wolfe article for the proposition that EAE may not be a proper model for treatment of multiple sclerosis in human patients. Applicant does not expressly claim treatment of human patients. Regardless, EAE is an established model for treatment of multiple sclerosis in animals as is well established by the prior art. The Pender and Wolfe article mentions only that some therapies which proved effective in EAE (mentioning γ-interferon, lenercept and altered peptide ligands) proved ineffective in humans. It is unclear what that statement in the article specifically refers to because the article then mentions several beneficial effects of γ-interferon on various aspects of MS in humans (see page 557 of Pender) and does not elaborate as to lenercept and altered peptide ligands. Further, it is well established that there is no requirement of human experimentation in order to obtain a patent. Regarding altered peptide ligands, the San Diego based company Neurocrine BioScience conducted an altered peptide ligand based trial for the treatment of multiple sclerosis that was terminated because of allergic reactions due to repetitive injections of high dose of the antagonist. Thus the failure of altered peptide ligand therapy appears related to dose and toxicity and not necessarily a problem of function. In fact, one of the purposes of using Ig for delivery in applicant's invention is to avoid repetitive injections. In

applicant's claimed invention where the T cell peptide is embedded in an immunoglobulin, because T cell peptides are hydrophobic, they are hidden from B cells and humoral responses will not develop. Thus, no IgE antibody will be produced and no allergic reactions will develop.

The PTO states that it is not clear that how the claimed invention as taught in the specification can "prevent" the activation of autoreactive T cells for a given T cell receptor antagonist. Applicant refers to paragraphs 8 and 9 of the Declaration of Zaghouani of July 2, 2001, submitted herein and Exhibit E thereto (Legge et al., J. Exp. Med. 185; 1043-1053 [1997]). As stated therein, the interaction between the antagonist/MHC complexes and the autoreactive T cells reduces cytokine production, thereby inactivating autoreactive T cells. The result is permanent elimination of disease symptoms. The phrase "preventing activation of autoreactive T cells" presumes from the time period forward after administration of the claimed composition.

For the reasons stated herein, applicant respectfully disagrees that it would require undue experimentation to practice the claimed invention. Ample guidance is provided in the specification in how to make and use the invention in combination with information already present at the time the application was filed without requiring "undue experimentation" as that phrase if defined in the Wands and Mineral Separation cases. Withdrawal of the rejection is respectfully requested.

3. Rejection over Deo under 35 USC 102(e)

Claims 1, 3 - 7 and 21 – 27 stand rejected under 35 USC 102(e) over U.S. Patent No. 5,837,243. However, applicant respectfully disagrees. First, it is important to note that the construct described in Deo, called "multispecific molecules", comprises an "anti-Fc receptor portion". According to Deo:

> An "anti-Fc receptor portion" refers to an antibody, a functional antibody fragment (e.g., Fab fragment) or a ligand that binds an Fc receptor on an effector cell. Preferred antibodies for use in the subject invention bind the Fc receptor on an effector cell on a site which is not bound by endogenous immunoglobulin. Most preferably, the anti-Fc receptor portion binds a human Fc gamma R (i.e., Fc.gamma RI, RII or RIII). Preferred humanized anti-Fc.gamma.R monoclonal antibodies are described in PCT application WO 94/103323 and U.S. Patent No. 4,954,617, the teachings of which are fully incorporated by reference.
>
> Col. 6, lines 1 – 11 of Deo.

Clearly, Deo's construct teaches the use of an antibody to bind to an Fc receptor on an effector cell. Deo teaches the engineering of peptides into the *constant domain* of the immunoglobulin. The method taught in Deo has limited applicability because of the diversity of Fc receptors and antibodies that would need to be made for each Fc receptor and the technology requires customization to individuals expressing particular Fc receptors. The constructs taught in Deo would likely destroy the Fc binding site on the Fc fragment incorporate with their peptides. Applicant's constructs are functionally very different and are based on the fact the Ig will bind to all Fc receptors and internalization is magnified without the need for customization.

In contrast to Deo, applicant's claimed construct requires part or all of a constant region of an immunoglobulin molecule which in turn binds and to the Fc receptor as its natural ligand. The construct is then endocytosed by the antigen presenting cell and presents the T cell receptor antagonists in association with endogenous MHC Class II molecules where they move to the antigen presenting cell surface and engage autoreactive T cells. Deo does not teach such a construct. The construct of Deo functions quite differently. In fact, in Example 7 of Deo, it teaches the use of a construct in a competitive mechanism by either the T cell antagonist occupying the MHC Class II molecules or T cell receptor binding or both to *inhibit* T cell activation. As stated in Deo, "The antagonist effects of APL TT833S and fusion protein Fab22-TT833S might be through competition at the level of MHC-binding or TCR-binding, or both." Col. 32, lines 15 – 17, Deo. However, this is not how applicant's claimed construct functions. In applicant's invention, the antagonistic peptides, once they are internalized into an antigen presenting cell, bind to newly synthesized MHC Class II molecules. The newly formed complexes move to the cell surface where they engage autoreactive T cells. The interaction between antagonist/MHC complexes and the autoreactive T cells reduces cytokine production, thereby inactivating autoreactive T cells (Declaration of Habib Zaghouani, submitted July 2, 2001 herein and Exhibit E thereto). Deo functions by a competitive mechanism and is unlikely to work because MHC molecules and pathogenic peptides are synthesized continuously in unlimited amounts (paragraph 9 of the Declaration of Habib Zaghouani, submitted July 2, 2001). There is no mechanism in Deo for "preventing activation of autoreactive T cells" as stated in the rejected claims. Thus applicant respectfully disagrees that the

claims are anticipated under 35 USC 102(e) by Deo and respectfully requests withdrawal of the rejection.

4. Rejection of claims 1, 5, 21 and 25 under 35 USC 103(a) over Deo in view of Karin et al.

Deo was discussed at length as to the anticipation rejection. As stated previously, Deo teaches the use of "multispecific molecules" comprising an "anti-Fc receptor portion" which is an antibody, or portion thereof, for binding to Fc gamma receptor of an effector cell. Example 7 of Deo teaches how the constructs of Deo may be used for inhibiting T cell activation.

Karin teaches the use of administering free myelin basic protein and variants to treat induced EAE in rats. Karin teaches vaccination for prevention. Applicant's method teaches therapy for suppression of ongoing disease. The experiments in Karin involved coinjecting healthy rats with a self antigen and a T cell receptor antagonist peptide. When the rats were injected with an EAE inducing peptide, EAE symptoms appeared for 7 days (see Table 2, pg. 2234). When the rats were coinjected with antagonist peptide, none of the rats developed symptoms altogether over the 7 day period. However, this is in contrast to the experiments of the present invention in which mice already suffering from EAE were injected with applicants claimed construct eliminated disease symptoms by inactivating autoreactive T cells. Karin's experiment involved administering T cell receptor antagonists derived from myelin basic protein to healthy animals along with an EAE producing protein, only to show that EAE symptoms did not appear. Karin also made no showing of permanent elimination of disease symptoms because the experiments only spanned 7 days. Karin's method teaches vaccination in order to prevent disease onset, applicant's invention teaches a therapy for suppression of ongoing disease. Thus there is no teaching or suggestion in Karin of permanently eliminating disease symptoms in all animals already suffering from disease by preventing T cell activation.

The combination of Deo in view of Karin does not obviate the claimed invention. Deo teaches a construct which functions in a very different manner to applicant's claimed construct. Deo's construct claims to inhibit T cell activation through a competitive mechanism through either competition at the level of MHC-binding or T cell receptor binding or both. Col. 32, lines 15 –

17, Deo. Deo does not teach or suggest a fusion protein that can alleviate symptoms associated with an autoimmune disorder by preventing activation of autoreactive T cells specific for said T cell receptor antagonist. Karin discloses the use of the administration of T cell receptor antagonist myelin basic protein and variants, not delivered in an immunoglobulin, for prevention of EAE. However, the claimed invention provides unexpected results over the combination of Deo in view of Karin in that it prevents activation of autoreactive T cells. Deo in view of Karin would not lead to such a result. Thus applicant respectfully disagrees that claims 1, 5, 21 and 25 are unpatentable under 35 USC 103(a) and respectfully requests withdrawal of the rejection.

5. Claims 1, 6, 21 and 26 stand rejected under 35 USC 103(a) as being unpatentable over Deo in view of Kuchroo et al.

Deo has been previously discussed at length. Kuchroo discloses the use of the T cell receptor antagonist myelin basic protein residues 139 – 151 and its analogue (leucine 144/arginine 147). Like Karin, the experiments of Kuchroo involved injecting healthy animals with self antigen and a T cell receptor antagonist peptide to monitor development of disease symptoms. The T cell receptor antagonist peptide was not delivered in an immunoglobulin but was administered as free peptide. Administration of the self antigen (which induces EAE) and the T cell receptor antagonist myelin basic protein analogue slowed down progression of the EAE disease symptoms in healthy mice, but approximately half of the treated mice in Kuchroo developed EAE after 25 days (see the lower panel of Figure 4 in Kuchroo). Thus, the administration of myelin basic protein analogue in mice only proved effective approximately half the time. Regardless, there is no teaching or suggestion in Kuchroo that the myelin basic protein analogues of Kuchroo would permanently eliminate disease symptoms in all treated subjects by preventing T cell activation. Thus, Deo in view of Kuchroo does not obviate the claimed invention. Deo at best shows a construct which seems to inhibit T cell activation through a competitive mechanism through competition at the level of MHC-binding or T cell receptor binding or both. Deo does not teach or suggest a fusion protein that can alleviate symptoms associated with an autoimmune disorder by preventing activation of autoreactive T cells specific for said T cell receptor antagonist. Kuchroo discloses the

administration of free myelin basic protein analogues for treatment of EAE administered in healthy animals, wherein in half of the treated animals disease symptoms returned. The claimed invention provides unexpected results over the combination of Deo in view of Kuchroo in that the claimed invention treats autoimmune disorders by preventing activation of autoreactive T cells in all treated subjects and is therefore nonobvious over the combination of Deo and Kuchroo. Thus applicant respectfully disagrees that claims 1, 5, 21 and 25 are unpatentable under 35 USC 103(a) over Deo in view of Kuchroo and respectfully requests withdrawal of the rejection.

6. Claims 1, 7, 21 and 27 stand rejected as being unpatentable under 35 USC 103(a) over Deo, in view of Elliot et al., Kuchroo and Karin

Deo, Kuchroo and Karin have been previously discussed. Elliot is concerned with epitope spreading and treating autoimmune disorders which involve multiple epitopes. Elliot teaches the use of a recombinant chimeric fusion protein MP4 that encodes multiple autoantigenic epitopes from isoforms of myelin basic protein and proteolipid protein. Similar to Kuchroo and Karin, the results of Elliot showed that treatment of healthy mice with the MP4 construct prevented onset of symptoms of EAE in mice after immunization with PLP or adoptive transfer of activated T cells. However, Elliot does not show elimination of disease in mice already suffering from EAE as demonstrated in applicant's invention. Elliot shows prevention of disease onset of EAE in healthy mice immunized with PLP 139 – 151, similar to the results of Karin and Kuchroo.

As previously discussed, Deo teaches the use of "multispecific molecules" comprising an "anti-Fc receptor portion" which is an antibody, or portion thereof, for binding to an Fc gamma receptor of an effector cell. Deo teaches the engineering of peptides into the constant domain of the immunoglobulin. Example 7 of Deo teaches how the constructs of Deo may be used for inhibiting T cell activation. However, nothing in Deo, Kuchroo or Karin teaches or suggests the use of multiple epitopes into an immunoglobulin as an approach for treating EAE. In fact Deo, Kuchroo and Karin teach away from this concept in their use of single epitopes. There is also no teaching or suggestion in Elliot for the engineering of multiple epitopes into an immunoglobulin backbone. To properly combine references, there must be some motivation or suggestion in either the prior art

references being combined or in the knowledge generally available to one of ordinary skill in the art, to combine the teachings. MPEP 706.02(j); In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438 (CAFC 1991). Applicant submits that there is no motivation or suggestion for the combination of references being asserted by the PTO.

However, even if the references are properly combined, the combination of Deo in view of Elliot in view of Kuchroo in view or Karin does not obviate claims 1, 7, 21 and 27. As stated previously as to Deo in view of Kuchroo and Deo in view of Karin, none of these references teach the claimed invention of treatment of autoimmune disorders by preventing activation of autoreactive T cells. There is nothing in Elliot that provides this missing teaching in order to properly reject applicant's claims under 35 USC 103(a).

Deo, Elliot, Kuchroo and Karin, taken separately or together, do not teach or suggest fusion proteins comprising T receptor antagonists linked to an immunoglobulin or portion thereof because none of the references teach or suggest that the compositions taught in the references would permanently eliminate disease symptoms by preventing T cell activation. Thus applicant respectfully disagrees that applicant's claimed invention is obviated over the asserted combinations of Deo, Elliot, Kuchroo and Karin. Applicant respectfully requests withdrawal of the rejection.

7. Rejection of claims 1, 3-4, 6, 21 – 24 and 25 under the judicially created doctrine of obviousness type double patenting over claims 1 – 16 of U.S. Patent No. 6,737,057.

Because applicant is uncertain of the final scope the claims, applicant respectfully requests the right to revisit the issue of double patenting over U.S. Patent No. 6,737,057 after the claims are allowed.

Applicant hereby respectfully requests a two month extension of time. If there are any

questions concerning this response, applicant's attorney can be reached at the number stated below.

Dated: 1/10/05 By: _____

John Wurst
Registration No. 40,283
(858) 410-5174